# Antihyperglycemic Activity of Novel Substituted 3*H*-1,2,3,5-Oxathiadiazole 2-Oxides

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A series of substituted 3*H*-1,2,3,5-oxathiadiazole-2-oxides (**6**) was prepared and tested for antihyperglycemic activity in the db/db mouse, a model for type 2 (non-insulin dependent) diabetes mellitus. The oxathiadiazoles **6** were synthesized by a two-step sequence: treatment of a substituted acetonitrile (**4**) with hydroxylamine to give the corresponding amidoxime (**5**) and cyclization with thionyl chloride to yield **6**. In terms of potency, the 2-naphthalenylmethyl group (as in compound **3**) was found to be the optimal substituent in this series. Compound **3** was approximately 5 times more potent than ciglitazone (**1**).

Multiple therapeutic approaches have been used to control the hyperglycemia associated with type 2 (non-insulin dependent) diabetes mellitus. Clinically, four divergent classes of drugs are in use, but each class possesses either significant liabilities or efficacy limitations. For example, sulfonylureas, such as chlorpropamide and glyburide, can induce dangerous hypoglycemia and are frequently ineffective.[1] The biguanides, phenformin and metformin, are associated with an increased incidence of lethal lactic acidosis.[2] Insulin can be an effective treatment for hyperglycemia of the type 2 diabetic patient, but the possibility of hypoglycemia and patient noncompliance are major difficulties.[3] The glucosidase inhibitors, such as acarbose, represent the newest therapeutic approach.[4] This class of compounds, however, can only reduce food-induced elevations of blood glucose and cannot alleviate fasting hyperglycemia.

There has been considerable effort in the last decade to develop orally active antihyperglycemic drugs that are devoid of the liabilities associated with available therapies. One approach of current interest is the improvement of insulin resistance. Ciglitazone (**1**) represents a prototype for compounds having such activity.[5] This compound normalizes plasma glucose in insulin-resistant animals by an as yet unknown mechanism, but does not induce hypoglycemia. The antihyperglycemic activity appears to be associated with the relatively acidic 2,4-thiazolidinedione moiety.[6] A number of compounds having potency equal to or greater than **1** have been prepared by utilizing this heterocycle,[7] including the (naphthlenylsulfonyl)-2,4-thiazolidinedione **2**.[7f] Other acidic heterocycles that have been used in antihyperglycemic compounds include the tetrazole[8a] and oxazolidine-2,4-dione[8b] rings.

Described in this paper is a structurally unique class of antihyperglycemic agents, which also contain an acidic heterocycle, the 3*H*-1,2,3,5-oxathiadiazole 2-oxide ring, appended via a methylene bridge to an aromatic ring system. Naphthalene has been identified as the optimal aromatic ring system in this series, as was found in the recently described sulfonyl-2,4-thiazolidinediones, e.g. **2**. Thus, in the genetically diabetic db/db mouse, an animal that exhibits many of the pathologies present in type 2 diabetes,[9] 4-[(2-naphthalenyl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-oxide (**3**) (AY-30,711) was found to be approximately 5 times as potent as ciglitazone (**1**).

## Chemistry

All of the oxathiadiazoles **6** described in this paper were prepared from a substituted acetonitrile **4** via a two-step reaction sequence: treatment with hydroxylamine hydrochloride and sodium methoxide in methanol to give an amidoxime **5**, followed by cyclization with thionyl chloride

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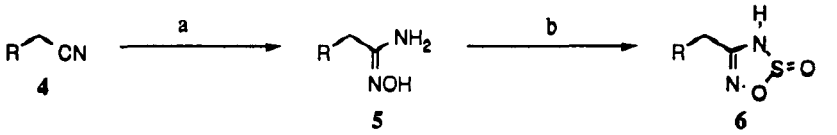
**Scheme I**[a]

Method A:

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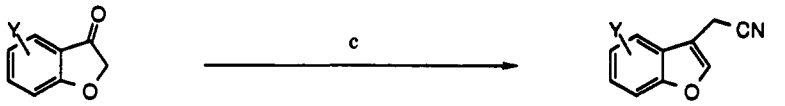
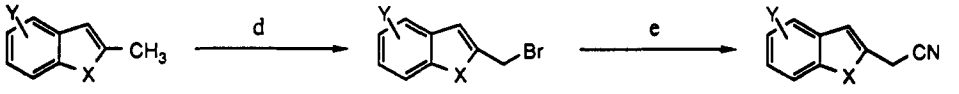
Method B:




**7a** (Y=H) **7e** (5-Cl,7-Cl)
**7b** (5-Cl) **7f** (5-Br)
**7c** (6-Cl) **7g** (5-$CH_3$)
**7d** (7-Cl)

**8a-8g**

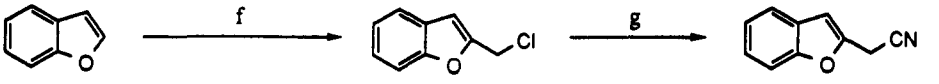
Method C:



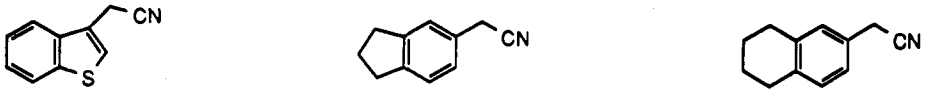

**9a** (X=O,Y=5-F) **9e** (S,5-F)
**9b** (O,6-F) **9f** (S,5-Cl)
**9c** (O,5-Cl) **9g** (S,5-Br)
**9d** (S,H)

**10a-10g** **11a-11g**

Method D:




12 13 14



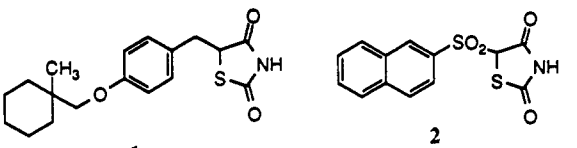

15 16 17

[a] (a) $H_2NOH$·HCl, NaOMe, MeOH. (b) $SOCl_2$, pyridine, $CH_2Cl_2$. (c) $(EtO)_2P(O)CH_2CN$, NaH, THF. (d) NBS, AIBN, $CCl_4$. (e) NaCN, KOH, $nBu_4NHSO_4$, $CHCl_3$, $H_2O$. (f) Paraformaldehyde, HCl, $H_2O$, benzene. (g) NaCN, DMSO.

and pyridine in dichloromethane[10] (Scheme I, method A). The acetonitriles were prepared as described below.

The (3-benzofuranyl)acetonitriles (**8**) were prepared from the 3(2*H*)-benzofuranones (**7**) by treatment with diethyl (cyanomethyl)phosphonate and sodium hydride (method B). Compounds **7b**,[11] **7f**,[12] and **7g**[13] were prepared by the method of Jung,[14] while **7c**,[11] **7d**,[11] and **7e**[15] were prepared according to Schroeder.[16] The (2-benzofuranyl)acetonitriles and (2-benzthiophenyl)acetonitriles (**11**) were prepared by *N*-bromosuccinimide bromination

**Chart I**

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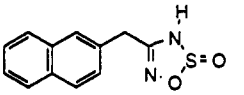


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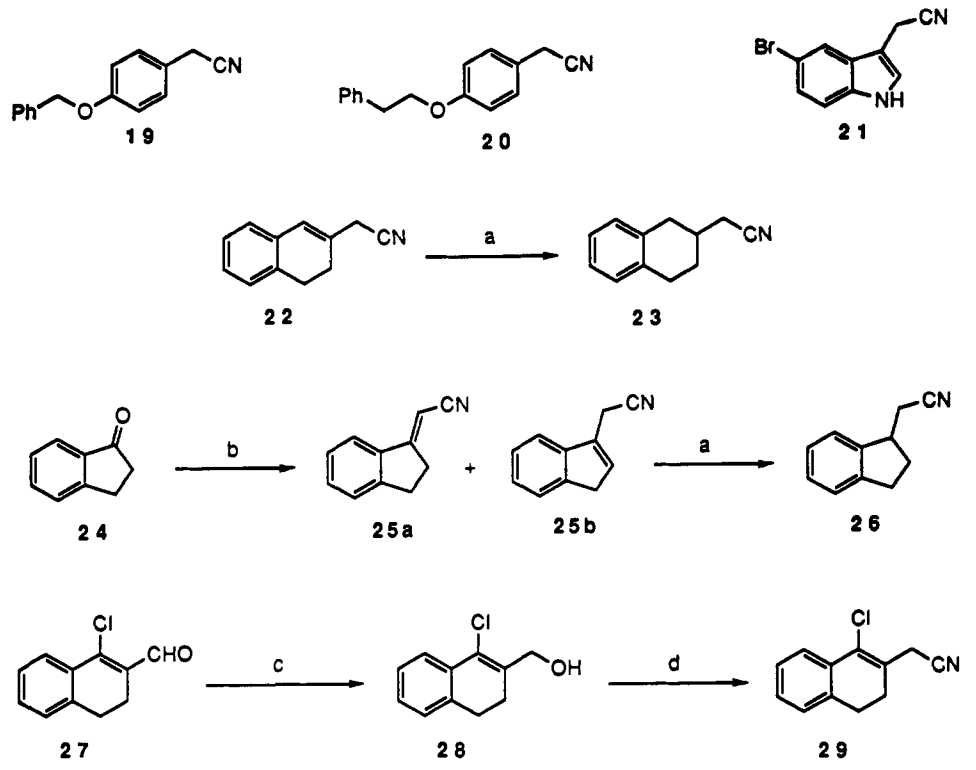
**Scheme II**[a]




[a] (a) $H_2$, 10% Pd/C, EtOH. (b) $(EtO)_2P(O)CH_2CN$, NaH, THF. (c) $NaBH_4$, MeOH, THF. (d) KCN, 18-crown-6, $nBu_3P$, $CCl_4$, acetonitrile.

of a 2-methylbenzofuran (**9a**,[17] **9b**, or **9c**[18]) or 2-methylbenzothiophene (**9d**,[18] **9e**,[19] **9f**,[18] or **9g**[20]) prepared according to Anderson,[18] and subsequent displacement with cyanide (method C). The chloromethylation and cyanide displacement reactions (method D) were utilized in the preparation of a number of acetonitriles, including (2-benzofuranyl)acetonitrile (**14**),[21] (3-benzthiophenyl)acetonitrile (**15**),[22] (5-indanyl)acetonitrile (**16**),[23] and ([6-(1,2,3,4-tetrahydronaphthalenyl]acetonitrile (**17**).[24]

[4-Hydroxyphenyl]acetonitrile (**18**) was used to prepare acetonitriles **19**[25] (benzyl bromide, potassium carbonate) and **20** (Mitsunobu reaction[26] with 2-phenylethanol; Scheme II). [3-(5-Bromoindolyl)]acetonitrile (**21**)[27] and [2-(3,4-dihydronaphthalenyl)]acetonitrile (**22**)[28] were prepared by literature methods. Compound **22** was converted to the tetrahydro analogue **23**[29] by catalytic hydrogenation (Scheme II) and [1-(2,3-dihydroindanyl)]acetonitrile (**26**)[30]

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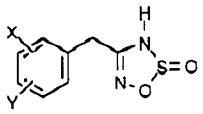
**Table I.** Benzyl-3*H*-oxathiadiazoles



| compd | X | Y | synthesis method | mp, °C | formula[a] | % decrease in plasma glucose[b] 20 mg/Kg | % decrease in plasma glucose[b] 100 mg/Kg |
|---|---|---|---|---|---|---|---|
| **30** | 3-$CF_3$ | H | A | 132–133 | $C_9H_7F_3N_2O_2S$ | [c] | −34 ± 9 |
| **31** | 3-Cl | H | A | 90–92 | $C_8H_7ClN_2O_2S$ | [c] | −40 ± 12[d] |
| **32** | 2-F | 4-Br | A | 124–125 | $C_8H_6BrFN_2O_2S$ | −17 ± 3[d] | −28 ± 3[d] |
| **33** | 4-$PhCH_2O$ | H | A | 165–166 | $C_{15}H_{14}N_2O_3S$ | [e] | [c] |
| **34** | 4-$PhCH_2CH_2O$ | H | A | 96–97 | $C_{16}H_{16}N_2O_3S$ | [c] | −56 ± 6[d] |
| **35** | 3-$CH_3$ | 4-$CH_3$ | A | 127–130 | $C_{10}H_{12}N_2O_2S$ | [c] | [c] |
| **36** | 4-tBu | H | A | 132–133 | $C_{12}H_{16}N_2O_2S$ | [c] | [c] |
| **37** | 4-Ph | H | A | 163–164 | $C_{14}H_{12}N_2O_2S$ | [c] | [c] |
| 1 | ciglitazone | | | | | [c] | −29 ± 7[f] |

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained. [b] Values (mean ± SE) are percent change relative to vehicle-treated group with use of 4-6 mice per group. [c] Less than −15% change. [d] $p < 0.05$. [e] Not tested. [f] Mean ± SD value of 34 experiments.

was prepared analogously. [2-(1-Chloro-3,4-dihydronaphthalenyl)]acetonitrile (**29**) was prepared from aldehyde **27**[31] by sodium borohydride reduction and conversion of the hydroxy group of **28** to a nitrile by the method of Mizuno et al.[32] (Scheme II).

## Results

Several substituted benzyloxathiadiazoles were examined in the postprandial assay in the db/db mouse (Table I). All of these compounds lowered plasma glucose by less than 15% at a dose of 20 mg/kg (po), except for **32**, which lowered plasma glucose by 17%. However, at the higher dose of 100 mg/kg, four compounds, **30**, **31**, **32**, and **34**, showed antihyperglycemic activity which was comparable to that of ciglitazone (**1**). Alkyl or aryl groups in the 4-position (**35–37**) were detrimental.

Various bicyclic heterocycles and carbocycles were then appended to the oxathiadiazole ring. The antihyperglycemic test results for these compounds are listed in Table II. All of the (benzofuranylmethyl)oxathiadiazoles, **38–48**, lowered plasma glucose by less than 15% at a dose of 20 mg/kg, except for the 7-chloro-substituted compound **41**, which lowered plasma glucose by 26%. At a dose of 100 mg/kg, the majority of the benzofuranylmethyl compounds decreased plasma glucose by greater than 15%, with the exception of **43** and **45**. Compound **41** remained the most potent at the higher dose, lowering plasma glucose by 54%. A reduction of 50–60% results in the normalization of plasma glucose levels in db/db mice. Of the (benzothienylmethyl)oxathiadiazoles, **49–53**, only the 5-bromo-substituted compound **53** had significant activity at a dose of 20 mg/kg, lowering plasma glucose by 20%. Again, most of the benzthiophenylmethyl compounds decreased plasma glucose by greater than 15% at the higher dose of 100 mg/kg. Compound **50**, which lowered plasma glucose by less than 15% at 20 mg/kg, appeared to be more potent than **53** at 100 mg/kg. **53** displayed a relatively flat dose response, with only a 29% reduction at the higher dose. Two (indolylmethyl)oxathiadiazoles, **54** and **55**, were prepared and tested. As in the case of the benzothienylmethyl compounds, the 5-bromo-substituted compound **55** was more active at a dose of 20 mg/kg. Compound **55** lowered plasma glucose by 22% at this dose, but showed a flat dose–response relationship like the (5-bromobenzothienyl)methyl compound **53**. Of the dihydroindanylmethyl- and tetrahydronaphthalenylmethyloxathiadiazoles **56–59**, only compound **59** lowered plasma glucose by greater than 15% (22% at the higher dose of 100 mg/kg). Finally, the dihydronaphthalenylmethyl and naphthalenylmethyl compounds **60**, **61**, and **3** displayed significant antihyperglycemic activity at a dose of 20 mg/kg (23%, 27%, and 37% reductions, respectively). Compounds **60** and **3** were also quite potent at 100 mg/kg (53% and 63% reductions, respectively).

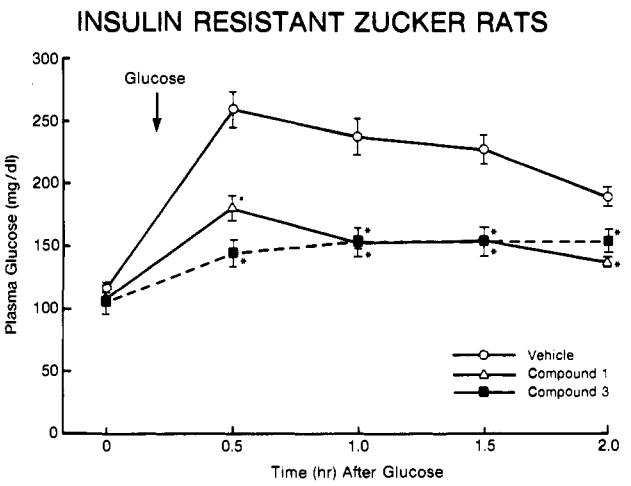



**Figure 1.** Compounds (100 mg/kg, po) or vehicle were administered to obese Zucker (fa/fa) rats 1 h prior to the glucose tolerance test (1 g/kg, sc). Blood samples were collected from the tail tip of unanesthetized rats. $N = 3$ rats per group (*) $p < 0.05$ versus vehicle group using Dunnett's multiple comparison test.

To assess the possible efficacy in a second animal model of diabetes, compound **3** was administered to obese Zucker (fa/fa) rats prior to a glucose tolerance test. As shown in Figure 1, compound **3** and ciglitazone caused a significant improvement in the glucose intolerance of these rats.

## Discussion

At the lower dose of 20 mg/kg, the majority of these compounds did not significantly lower plasma glucose in the db/db mouse. Of the benzofuranylmethyl, benzothienylmethyl, and indolylmethyl compounds, only **41**, **53**, and **55** decreased plasma glucose by more than 15%. A

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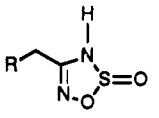
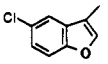
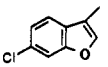
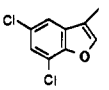
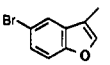
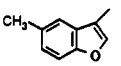
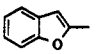
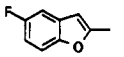
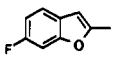
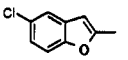
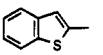
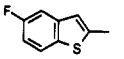
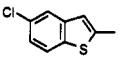
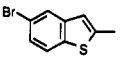
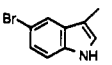
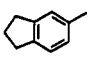
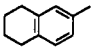
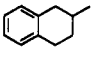
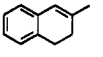
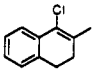
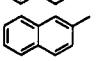
**Table II.** Bicyclic Oxathiadiazoles



| compd | R | synthesis method | mp, °C | formula[a] | % decrease in plasma glucose[b] 20 mg/Kg | % decrease in plasma glucose[b] 100 mg/Kg |
|---|---|---|---|---|---|---|
| 38 |  | A,B | 139–140 | $C_{10}H_8N_2O_3S$ | *c* | −28 ± 11 |
| 39 |  | A,B | 140–141 | $C_{10}H_7ClN_2O_3S$ | *c* | *e* |
| 40 |  | A,B | 161–162 | $C_{10}H_7ClN_2O_3S$ | *c* | −22 ± 3 |
| 41 |  | A,B | 160–162 | $C_{10}H_7ClN_2O_3S$ | −26 ± 7[d] | −54 ± 2[d] |
| 42 |  | A,B | 170–172 | $C_{10}H_6Cl_2N_2O_3S$ | *c* | −29 ± 4[d] |
| 43 |  | A,B | 144–145 | $C_{10}H_7BrN_2O_3S$ | *c* | *c* |
| 44 |  | A,B | 152–153 | $C_{11}H_{10}N_2O_3S$ | *c* | −42 ± 4[d] |
| 45 |  | A,D | 133–135 | $C_{10}H_8N_2O_3S$ | *c* | *c* |
| 46 |  | A,C | 144–145 | $C_{10}H_7FN_2O_3S$ | *c* | −25 ± 7[d] |
| 47 |  | A,C | 155–156 | $C_{10}H_7FN_2O_3S$ | *c* | −18 ± 5 |
| 48 |  | A,C | 148–149 | $C_{10}H_7ClN_2O_3S$ | *c* | −23 ± 4 |
| 49 |  | A,D | 134–136 | $C_{10}H_8N_2O_2S_2$ | *c* | −30 ± 2[d] |
| 50 |  | A,C | 127–129 | $C_{10}H_8N_2O_2S_2$ | *c* | −42 ± 4[d] |
| 51 |  | A,C | 156–157 | $C_{10}H_7FN_2O_2S_2$ | *c* | *c* |
| 52 |  | A,C | 155–156 | $C_{10}H_7ClN_2O_2S_2$ | *c* | −24 ± 6 |
| 53 |  | A,C | 156–157 | $C_{10}H_7BrN_2O_2S_2$ | −20 ± 6[d] | −29 ± 7[d] |
| 54 |  | A | 124–125 | $C_{10}H_8N_3O_2S$ | *c* | −22 ± 10 |
| 55 |  | A | 125–126 | $C_{10}H_8BrN_3O_2S$ | −22 ± 4[d] | −30 ± 5[d] |
| 56 |  | A,D | 122–123 | $C_{11}H_{12}N_2O_2S$ | *c* | *c* |
| 57 |  | A | 104–106 | $C_{11}H_{12}N_2O_2S$ | *c* | *c* |
| 58 |  | A,D | 146–148 | $C_{12}H_{14}N_2O_2S$ | *c* | *c* |
| 59 |  | A | 123–124 | $C_{12}H_{14}N_2O_2S$ | *c* | −22 ± 7[d] |
| 60 |  | A | 118–120 | $C_{12}H_{12}N_2O_2S$ | −23 ± 3[d] | −53 ± 5[d] |
| 61 |  | A | 91–92 | $C_{12}H_{11}ClN_2O_2S$ | −27 ± 3[d] | *e* |
| 3 |  | A | 145–147 | $C_{12}H_{10}N_2O_2S$ | −37 ± 2[d] | −63 ± 1[d] |

[a] Satisfactory C, H, and N elemental analyses (±0.4%) were obtained. [b] Values (mean ± SE) are percent changes relative to vehicle-treated group with use of 4–6 mice per group. [c] Less than −15% change. [d] $p < 0.05$. [e] Not tested.

common feature among these compounds is either a chloro or bromo substituent: 7-chloro in **41** and 5-bromo in **53** and **55**. While these halogen substituents increase lipophilicity, the position of the substituent also seems to be important; a 5-chloro group did not enhance activity with these substrates (compounds **39**, **48**, and **52**) nor did a 5-bromo group in the case of the 3-benzofuranylmethyl compound **43**.

Among the carbocycles examined, the most potent activity was observed in the naphthalenyl analogues. Significant activity was retained upon partial saturation to the dihydronaphthalenyl group (compounds **60** and **61**) but activity was decreased on further saturation (compounds **58** and **59**). The activity demonstrated by **60** and **61** may in part result from their metabolic transformation to **3**. No definitive evidence for this type of metabolism was obtained, but oxidations at benzylic carbons have been well documented.[37] These results and those for the benzyl compounds together suggest that a planar bicyclic system is the optimal ring system for attachment to the oxathiadiazole. The addition of a halogen substituent to the benzofuran, benzothienyl, and indolyl compounds improved activity in some cases, and such a strategy is expected to prove fruitful when applied to the naphthalenyl group of **3**. Work in this area is ongoing.

Although ciglitazone (**1**), the reference compound used in the biologic assay, improves the insulin sensitivity of diabetic mice,[5] other compounds that have diverse antihyperglycemic mechanisms of action are equally effective. The hyperglycemia of the db/db mice can be reduced by inhibition of or interference with fatty acid oxidation, glucosidase activity, renal tubular glucose reabsorption, or gluconeogenesis.[33] Experiments to elucidate the mechanism of action of the oxathiadiazoles are in progress, and therefore it is not known if the compounds improve insulin sensitivity in a manner similar to that of the thiazolidinediones. However, it should be noted that in preliminary studies, some of the oxathiadiazoles induced glucosuria in normal mice. The relevance of this action to the antihyperglycemic efficacy is not known.

In summary, the 3*H*-oxathiadiazole 2-oxide heterocycle has been identified as a novel pharmacophore which, when appended to a bicyclic aromatic system via a methylene bridge, brings about a significant reduction in the elevated plasma glucose levels of diabetic db/db mice.

## Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The NMR spectra were recorded on a Varian VXR200 or a Bruker AM-400 instrument. The infrared spectra were recorded on a Perkin-Elmer diffraction grating or a Perkin-Elmer 784 spectrophotometer. The mass spectra were recorded on a LKB-9000S or a Finigan 8230 high-resolution mass spectrometer. Merck silica gel (70–230 mesh) was used for column chromatography. Organic extracts were dried over $MgSO_4$.

**Method A. 4-[(2,3-Dihydro-1*H*-inden-5-yl)methyl]-3*H*-1,2,3,5-oxathiadiazole 2-Oxide (56).** A stirred mixture of sodium methoxide (25 wt% in methanol; 16.0 mL, 0.070 mol), hydroxylamine hydrochloride (4.9 g, 0.07 mol), and methanol (60 mL) was heated under reflux for 30 min. (5-Indanyl)acetonitrile (**16**)[23] (10.0 g, 0.064 mol) was added and heating was continued for 18 h. The mixture was concentrated and partitioned between water and ether. The organic phase was dried and concentrated to give 11.4 g of a yellow oil. The crude product was purified by flash chromatography (20% EtOAc/hexane; 50% EtOAc/hexane) to give 6.5 g (54%) of **5** (R = 5-indanyl) as a pale yellow solid: mp 60 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.06 (m, 2 H), 2.88 (t, $J$ = 7.5 Hz, 4 H), 3.43 (s, 2 H), 4.51 (br s, 2 H), 6.40 (br s, 1 H), 7.14 (m, 3 H). Anal. ($C_{11}H_{14}N_2O$) C, H, N.

To a cooled (0 °C), stirred mixture of **5** (R = 5-indanyl; 6.5 g, 0.034 mol), pyridine (5.4 g, 0.068 mol), and $CH_2Cl_2$ (35 mL) was added a solution of thionyl chloride (4.5 g, 0.038 mol) in $CH_2Cl_2$ (10 mL) over 20 min. Stirring was continued for 20 min and the mixture was concentrated. Water (100 mL) was added and the solid was collected by filtration. Recrystallization from ether (3 times) gave 720 mg (9%) of **56** as pale yellow needles: mp 122–123 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.07 (m, 2 H), 2.89 (t, $J$ = 7.4 Hz, 4 H), 3.84 (d, $J$ = 15.8 Hz, 1 H), 3.98 (d, $J$ = 15.8 Hz, 1 H), 7.02 (d, $J$ = 7.6 Hz, 1 H), 7.05 (br s, 1 H), 7.12 (s, 1 H), 7.21 (d, $J$ = 7.6 Hz, 1 H); IR (KBr, cm$^{-1}$) 3120 (NH); MS $m/e$ 236 ($M^+$). Anal. ($C_{11}H_{12}N_2O_2S$) C, H, N.

**Method B. [3-(7-Chlorobenzofuranyl)]acetonitrile (8d).** To a stirred suspension of NaH (50% dispersion in mineral oil, washed with hexane; 1.82 g, 0.038 mol) in THF (70 mL) was added a solution of diethyl (cyanomethyl)phosphonate (6.7 g, 0.038 mol) in THF (30 mL) dropwise over 20 min. After an additional 20 min, the mixture was cooled to 0 °C and a solution of 7-chloro-3-benzofuranone (**7d**)[11] (5.8 g, 0.034 mol) in THF (80 mL) was added dropwise over 30 min. The cooling bath was removed and stirring was continued at room temperature for 18 h. Water (400 mL) and ether were added. The organic phase was washed with brine, dried, and concentrated to give 6.4 g (97%) of **8d** as a red solid. Recrystallization from ether/hexane gave off-white needles: mp 76–77 °C; $^1$H NMR ($CDCl_3$) $\delta$ 3.77 (s, 2 H), 7.26 (dd, $J$ = 7.5 Hz, 7.5 Hz, 1 H), 7.39 (dd, $J$ = 7.5 Hz, 1.2 Hz, 1 H), 7.50 (dd, $J$ = 7.5 Hz, 1.2 Hz, 1 H), 7.74 (s, 1 H). Anal. ($C_{10}H_6ClNO$) C, H, N.

**Method C. [2-(5-Chlorobenzothienyl)]acetonitrile (11f).** To a heated (reflux) mixture of *N*-bromosuccinimide (14.7 g, 0.083 mol) and $CCl_4$ (400 mL) was added AIBN (0.8 g, 0.005 mol). After 30 s, a solution of 5-chloro-2-methylbenzothiophene (**9f**)[18] (15.1 g, 0.083 mol) in $CCl_4$ (30 mL) was added all at once. Heating was continued for 24 h. The mixture was cooled and filtered, and the filtrate was concentrated to give 22.4 g (>100%) of **10f**[19] as a yellow solid. The crude product was used directly in the next reaction: $^1$H NMR ($CDCl_3$) $\delta$ 4.75 (s, 2 H), 7.30 (m, 2 H), 7.70 (m, 2 H).

To a stirred solution of **10f** (1.00 g, 3.82 mmol) in $CHCl_3$ (1 mL) was added a mixture of NaCN (0.20 g, 4.00 mmol), KOH (62 mg, 0.96 mmol), $nBu_4NHSO_4$ (0.33 g, 0.96 mmol), and water (1 mL). After 1 h at room temperature, the mixture was heated under reflux for 30 min, cooled, and partitioned between $CHCl_3$ and water. The aqueous phase was extracted with $CHCl_3$, and the combined organic phases were washed with 2 N HCl and saturated aqueous $NaHCO_3$, dried, and concentrated. Purification by flash chromatography (20% ether/hexane) gave 214 mg (27%) of **11f**[34] as a yellow solid: mp 160–162 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.00 (s, 2 H), 7.20 (s, 1 H), 7.30 (m, 1 H), 7.72 (m, 2 H); IR (KBr, cm$^{-1}$) 2250 (CN).

**Method D. (2-Benzofuranyl)acetonitrile (14).** A cooled (0 °C), stirred mixture of paraformaldehyde (15.2 g), benzene (55 mL), and concentrated HCl (84 mL) was saturated with HCl gas. Benzofuran **12** (20.0 g, 0.17 mol) was added, and the resulting mixture was stirred at room temperature for 1.5 h. The mixture was recooled, ether was added, and the layers were separated. The organic phase was washed with water and saturated aqueous $NaHCO_3$, dried, and concentrated. The crude product was com-

(33) (a) Tutwiler, G. F.; Kirsch, T.; Mohrbacher, R. J.; Ho, W. Pharmacologic Profile of Methyl 2-Tetradecylglycidate (McN-3716). An Orally Effective Hypoglycemic Agent. *Metabolism* **1978**, *27*, 1539–1556. (b) Lee, S. M. The Effect of Chronic $\alpha$-Glycosidase Inhibition of Diabetic Nephropathy, in the *db/db* Mouse. *Diabetes* **1982**, *31*, 249–254. (c) Ortlepp, I.; Gaertner, K.; Schoetz, H.; Zogbaum, A. Chronic Phlorizin Intoxication in Adipose Mutant Mice C57BL/KS db/db and in Normal Controls. In *New Developments in Biosciences: Their Implications for Laboratory Animal Science*; Beynen, A. C., Solleveld, H. A., Eds.; Martin Nijhoff: Dordrecht, 1988; pp 359–363. (d) Hanson, R. L.; Ho, R. S.; Wiseberg, J. J.; Simpson, R.; Younathan, E. S.; Blair, J. B. Inhibition of Gluconeogenisis and Glycogenolysis by 2,5-Anhydro-D-mannitol. *J. Biol. Chem.* **1984**, *259*, 218–223.

(34) Chapman, N. B.; Clarke, K.; Humphries, A. J.; Saraf, S. U.-D. Pharmacologically Active Benzo[*b*]thiophene Derivatives. Part VII. Analogues of Tryptamine and Heteroauxin. *J. Chem. Soc. C* **1969**, 1612–1616.

bined with similarily prepared material and distilled under high vacuum to give four fractions. The fourth fraction contained 7.9 g (22%) of 13[35] as a colorless oil: bp 95 °C (0.6 mm); $^1$H NMR ($CDCl_3$) δ 4.70 (s, 2 H), 6.74 (s, 1 H), 7.27 (m, 2 H), 7.49 (d, $J$ = 8.7 Hz, 1 H), 7.54 (d, $J$ = 8.6 Hz, 1 H).

To a stirred, partial solution of NaCN (2.8 g, 0.057 mol) in DMSO (17 mL) was added 13 (7.9 g, 0.047 mol) over 20 min. The mixture was stirred at room temperature for 18 h and then partitioned between ether and water. The organic phase was washed with water, brine, dried, and concentrated to give a brown oil. The crude product was distilled bulb-to-bulb under high vacuum (0.6 mm) to give 4.6 g (61%) of 14[21] as a yellow solid: mp 48–50 °C; $^1$H NMR ($CDCl_3$) δ 3.91 (s, 2 H), 6.74 (s, 1 H), 7.27 (m, 2 H), 7.46 (d, $J$ = 8.0 Hz, 1 H), 7.55 (d, $J$ = 6.6 Hz, 1 H); IR (KBr, $cm^{-1}$): 2260 (CN).

**[4-(Benzyloxy)phenyl]acetonitrile (19).** A mixture of (4-hydroxyphenyl)acetonitrile (18) (8.3 g, 0.062 mol), benzyl bromide (10.6 g, 0.062 mol), potassium carbonate (8.6 g, 0.062 mol), and acetone was heated under reflux for 17 h. The mixture was filtered and the filtrate was concentrated to give 13.3 g (97%) of 19[25] as a white solid: $^1$H NMR (DMSO-$d_6$) δ 3.90 (s, 2 H), 5.06 (s, 2 H), 7.03 (d, $J$ = 8.6 Hz, 2 H), 7.25 (d, $J$ = 8.6 Hz, 2 H), 7.40 (m, 5 H).

**[4-(2-Phenylethoxy)phenyl]acetonitrile (20).** To a solution of 18 (5.0 g, 0.038 mol), 2-phenylethanol (5.0 g, 0.041 mol), and triphenylphosphine (11.8 g, 0.045 mol) in THF (100 mL) was added diethyl azodicarboxylate (7.9 g, 0.045 mol). The mixture was stirred at room temperature for 24 h. Water was added and the mixture was extracted with ether. The combined extracts were washed with water and brine, dried, and concentrated to give an oily yellow solid. Trituration with ether and concentration of the filtrate gave a yellow oil. Purification by flash chromatography (20% EtOAc/hexane) gave 5.9 g (66%) of 20 as a pale yellow oil: $^1$H NMR (DMSO-$d_6$) δ 3.00 (t, $J$ = 7.0 Hz, 2 H), 3.90 (s, 2 H), 4.18 (t, $J$ = 7.0 Hz, 2 H), 6.93 (d, $J$ = 8.7 Hz, 2 H), 7.25 (d, $J$ = 8.7 Hz, 2 H), 7.30 (m, 5 H).

**[2-(3,4-Dihydronaphthalenyl)]acetonitrile (22).** To a mechanically stirred suspension of NaH (50% dispersion in mineral oil, washed with hexane; 9.0 g, 0.19 mol) in THF (400 mL) was added diethyl (cyanomethyl)phosphonate (33.1 g, 0.19 mol) dropwise. After 30 min, the mixture was cooled to 0 °C and a solution of 2-tetralone (24.8 g, 0.17 mol) in THF (100 mL) was added. The resulting mixture was stirred at room temperature for 1 h. Water was added and the mixture was extracted with ether. The combined extracts were washed with brine, dried, and concentrated to give an orange oil. Bulb-to-bulb distillation under high vacuum (0.6 mm) yielded 22.7 g (79%) of 22[28] as a colorless oil: $^1$H NMR ($CDCl_3$) δ 2.34 (t, $J$ = 8.2 Hz, 2 H), 2.90 (t, $J$ = 8.2 Hz, 2 H), 3.28 (s, 2 H), 6.75 (s, 1 H), 7.18 (m, 4 H).

**[2-(1,2,3,4-Tetrahydronaphthalenyl)]acetonitrile (23).** A solution of 22 (11.0 g, 0.065 mol) in ethanol (400 mL) was hydrogenated (50 psi) over 10% Pd/C (1.1 g) for 6 h. The catalyst was removed by filtration and the filtrate was concentrated to give 10.6 g (95%) of 23[29] as a colorless oil: $^1$H NMR ($CDCl_3$) δ 1.56 (m, 1 H), 2.00–2.30 (m, 2 H), 2.45 (d, $J$ = 7.0 Hz, 2 H), 2.80–3.10 (m, 4 H), 7.11 (m, 4 H).

**(5-Indanyl)acetonitrile (26).** Compound 26[30] was prepared in a similar manner to 23 (above) from a mixture of 25a and 25b:[36] $^1$H NMR ($CDCl_3$) δ 1.90 (m, 2 H), 2.30–3.10 (m, 4 H), 3.5 (m, 1 H), 7.23 (m, 4 H).

**[2-(1-Chloro-3,4-dihydronaphthalenyl)]acetonitrile (29).** To a cooled (0 °C) mixture of $NaBH_4$ (2.8 g, 0.075 mol) and methanol (150 mL) was added a solution of 1-chloro-3,4-dihydro-2-naphthaldehyde (27)[31] (9.6 g, 0.050 mol) in THF (150 mL). After 1 h, $CO_2$ was bubbled into the solution for 15 min. The mixture was concentrated and partitioned between water and ether. The organic phase was dried and concentrated to give 9.9 g (100%) of 28 as a yellow oil: $^1$H NMR ($CDCl_3$) δ 1.63 (br s, 1 H), 2.60 (t, $J$ = 8.2 Hz, 2 H), 2.85 (t, $J$ = 8.2 Hz, 2 H), 4.50 (s, 2 H), 7.05–7.30 (m, 3 H), 7.63 (d, $J$ = 8.6 Hz, 1 H).

According to the procedure of Mizuno,[32] a mixture of powdered KCN (5.99 g, 0.092 mol), 18-crown-6 (1.22 g, 0.0046 mol), 28 (8.9 g, 0.046 mol), tri-$n$-butylphosphine (12.71 mL, 0.051 mol), and $CCl_4$ (4.92 mL, 0.051 mol) in acetonitrile (180 mL) was stirred at room temperature for 18 h. The mixture was diluted with ether (300 mL) and washed with water and brine, dried, and concentrated to give a brown oil. Purification by flash chromatography (20% EtOAc/hexane) gave 2.11 g (23%) of 29 as a yellow oil: $^1$H NMR ($CDCl_3$) δ 2.61 (t, $J$ = 7.7 Hz, 2 H), 2.95 (t, $J$ = 7.7 Hz, 2 H), 3.61 (s, 2 H), 7.12–7.35 (m, 3 H), 7.61 (m, 1 H).

**Pharmacological Procedures.** On the morning of day 1 (baseline), 35 mice [male, db/db (C57BL/KsJ), Jackson Laboratories, 2–7 months of age and 35–60 g] were fasted for 4 h, weighed, and a baseline blood sample was collected from the tail tip of each mouse without anesthesia, placed directly into a fluoride-containing tube, mixed, and maintained on ice. Food was then returned to the mice. The plasma was separated and the levels of glucose in the plasma were determined by an Abbott VP Analyzer. Because of the variable plasma glucose levels of the db/db mice, the five mice having the most extreme (i.e., highest or lowest) plasma glucose levels were excluded and the remaining 30 mice were randomly assigned into 7 groups of equivalent mean plasma glucose level (vehicle control, ciglitazone, and 5 drug groups). On the afternoon of days 1, 2, and 3 the vehicle (0.2 mL of 2% Tween 80/saline w/v) or drugs were administered (po) to the ad libitum fed mice. On the morning of day 4, the food was removed from the cages for 3 h, a blood sample was collected, and the mice were then given the fourth administration of drug or vehicle. Additional blood samples were collected at 2 and 4 h after drug administration. Plasma glucose levels were determined.

To assess drug activity, the percent change of an animal's plasma glucose level on day 4 (mean of the 2- and 4-h values) from its level before drug administration (day 1 baseline sample) was determined as follows:

$$\frac{\text{mean of 2- and 4-h samples (day 4)}}{\text{baseline sample (day 1)}} \times 100$$

A 50–60% reduction of plasma glucose levels in the hyperglycemic db/db mice represented a normalization of glucose levels.

Analysis of variance followed by Dunnett's multiple comparison (one-sided) was used to estimate the degree of statistical significance of the difference between the vehicle group and the individual groups.

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128104-36-9; **20** amidoxime, 128104-37-0; **21**, 774-14-1; **21** amidoxime, 128104-92-7; **22**, 63625-95-6; **22** amidoxime, 128104-88-1; **23**, 128104-99-4; **23** amidoxime, 139346-95-5; **24**, 83-33-0; **25a**, 10426-30-9; **25b**, 10381-08-5; **26**, 26452-99-3; **26** amidoxime, 139346-96-6; **27**, 3262-03-1; **28**, 128104-82-5; **29**, 128104-83-6; **29** amidoxime, 128104-84-7; **30**, 128104-43-8; **31**, 128104-42-7; **32**, 128104-44-9; **33**, 128104-47-2; **34**, 128104-41-6; **35**, 128104-40-5; **36**, 128104-51-8; **37**, 128104-52-9; **38**, 128104-98-3; **39**, 128105-08-8; **40**, 128105-10-2; **41**, 128105-02-2; **42**, 128105-11-3; **43**, 128105-09-9; **44**, 128105-12-4; **45**, 128105-17-9; **46**, 128105-06-6; **47**, 139346-97-7; **48**, 139346-98-8; **49**, 128105-16-8; **50**, 128105-15-7; **51**, 128129-37-3; **52**, 128105-14-6; **53**, 128105-05-5; **54**, 128104-89-2; **55**, 128105-04-4; **56**, 128105-13-5; **57**, 139346-99-9; **58**, 139347-00-5; **59**, 128129-36-2; **60**, 128105-03-3; **61**, 128105-01-1; $(EtO)_2P(O)CH_2CN$, 50586-62-4; benzyl bromide, 100-39-0; 2-phenylethanol, 60-12-8; 2-tetralone, 530-93-8; (4-hydroxyphenyl)acetonitrile, 14191-95-8.

# Synthesis and Antiulcer Activity of Novel 5-(2-Ethenyl substituted)-3(2*H*)-furanones

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In order to investigate new antiulcer agents, spizofurone 1 (AG-629) was fragmented and reassembled to generate 5-phenyl-2,2-dimethyl-3(2*H*)-furanone (bullatenone, **2**). Because of the antiulcer activity of **2**, 5-phenyl-substituted 2,2-dimethyl-3(2*H*)-furanones (**3–6**) were made and shown to have poor activity. Insertion of an ethenyl link between the furanone and phenyl rings gave 5-(2-phenylethenyl)-2,2-dimethyl-3(2*H*)-furanone (**7**). This compound had better activity than **2**. Compounds **8–41** were synthesized to evaluate the SAR in 5-(2-ethenyl substituted)-3(2*H*)-furanones. Electron-withdrawing substituents on the aromatic ring (**8**, **10**, **19**, and **20**) gave 2–3-fold higher activity. Further increases in the activity were found when the phenyl ring was replaced by heterocyclic nuclei. Compounds that contained a thiophene (**29**), pyridine (**24–26**), or quinoline ring (**32**) had the best activity. Replacement of the methyl group on the furanone ring with a phenyl (**34**) or *p*-fluorophenyl (**40**) substituent in the 2-pyridine series gave compounds with activity that ranked with the best obtained in this study. The best compounds from the above SAR studies were evaluated in the ethanol-necrosis model for duration of cytoprotection action. Compounds **19**, **24**, and **29**, which had the best duration of action, were tested with AG-629 in the acidified aspirin and indomethacin-induced lesion models. Only compound **24** had equivalent activity with AG-629 in both models.

## Introduction

The stomach is constantly subjected to a variety of pathogenetic factors, including its own acid-pepsin secretion, microorganisms and, sometimes, alcohol and irritant drugs. Nevertheless, until recently, the primary strategy in ulcer therapy had focused on only the inhibition of gastric acid secretion. One successful approach to decreasing stomach acid secretion is to antagonize the parietal cell $H_2$ (histamine) receptor. Considerable drug discovery efforts led to the development of several $H_2$ antagonists as marketable drugs, which controlled 90% of the 1988 antiulcer market.[1] Although the therapeutic and commerical success of $H_2$ antagonists has been remarkable, some ulcer patients do not respond to gastric secretion inhibitors. Furthermore, it is well known that most patients with gastric ulcers or gastritis have acid secretory rates in the normal range.[2] Also, many gastric ulcer patients with normal or lower than normal acid secretion have deficient mucosal bicarbonate barrier[3] or mucosal blood flow.[4]

Concurrent with the development of $H_2$ antagonists, Robert[5,6] observed that the property of certain prostaglandins to inhibit gastric secretion and to protect against experimentally-induced lesions could be separated from each other by dose. When the prostaglandin dose caused mucosal protection but no gastric secretion inhibition, this phenomenon was called cytoprotection.[7] This initial concept has been redefined to designate the target area, such as gastroprotection or gastric mucosal protection, because an absolute mucosal cell preservation has not been demonstrated.[2,8] The inability of some patients to respond to most inhibitors of gastric acid secretion, coupled with the above observations, stimulated interest in the search for antiulcer drugs that might act by strengthening gastric and duodenal mucosal defenses. This premise was realized in sucralfate,[9] which captured 10% of the 1988 antiulcer market.[1] Another gastroprotective agent, spizofurone (AG-629, **1**), is also reputed to be a weak antisecretory agent with strong gastroprotective properties.[10] This drug

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